SUPPORT FOR THE AMENDMENTS

The amendments to Claim 1 and newly added Claims 20-29 are supported by the specification at pages 4-60 and by original Claim 12, particularly the paragraphs bridging pages 6-7 and 7-8, and Table 1 of the present specification. Claims 2 and 11 have been amended to make a grammatical change. No new matter is believed to have been added to this application by these amendments.

REMARKS

Claims 1-3, 11, and 20-29 are now pending. Favorable reconsideration is respectfully requested.

The present invention relates to a method of treating cachectic condition caused by cancers, diabetes, gastrointestinal inflammatory diseases, chronic rheumatoid arthritis, hepatitis, hepatic cirrhosis, hypersensitive interstitial pneumonia, pulmonary fibrosis or autoimmune inflammatory diseases, comprising administering to a patient in need thereof an effective amount of a composition comprising a substance, wherein said substance (a) reduces the content of reductive glutathione in macrophages in said patient, (b) suppresses cellular immune responses in said patient, (c) increases IL-6 production by macrophages in said patient, and (d) decreases IL-12 and NO production by macrophages in said patient. See Claim 1.

An important feature of the present invention is the finding that reducing the content of reductive glutathione in macrophages leads to an increase in IL-6 production and a decrease in IL-12 and NO production by macrophages, thereby skewing Th1/Th2 balance to Th2. It is known that the Th1/Th2 balance controls the balance between humoral and cellular immunity, and the Inventors have discovered that the Th1/Th2 balance is regulated by the

redox state of the macrophages and that the redox state of the macrophages plays an important role in regulating the cellular vs. humoral immune responses in a wide range of immunological diseases.

The rejection of the claims for obviousness-type double patenting over U.S. Patent No. 6,197,749 is obviated by the Terminal Disclaimer submitted herewith. Accordingly, withdrawal of this ground of rejection is respectfully requested.

At the outset, Applicants appreciate the Examiner's indication that claims reciting "cystine derivatives" are enabled.

As discussed above, the present invention was made by a series of findings that the Th1/Th2 balance is regulated by the redox state of macrophages, that the redox state of the macrophages plays an important role in regulating the cellular vs. humoral immune responses in a wide range of immunological diseases, and that reducing the content of the reductive glutathione in macrophages leads to an increase of IL-6 production and a decrease of IL-12 and NO production macrphages, thereby skewing the Th1/Th2 balance to Th2. Although cystine derivatives are used a material for reducing the content of reductive glutathione in macriphages, the present application provides sufficient basis that any substance which reduces the content of reductive glutathione in macrophages are operative in the same manner as cystine deriviatives, when it is administered in an effective amount to increase IL-6 prouction and decrease IL-12 and NO by macrophages.

Based on the foregoing, the pending claims are enabled. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 3 and 11 under 35 U.S.C. §112, second paragraph, is believed to be obviated by the amendment submitted above in part and is, in part, respectfully traversed.

The present specification provides a detailed description examples of the cystine deriviative recited in Claim 3 at pages 9-10. Based on this detailed description, one reading Claim 3 in light of the specification would readily appreciate the meaning of this term.

As amended above, Claim 11 recites, *inter alia*, that the substance is "a conjugate of a cytotoxic DNA alkylating agent with glutathione." The present specification also provides a detailed description of such compounds at page 9, lines 6-15. Based on these detailed descriptions in the specification, the meaning of Claim 11 is readily apparent to one skilled in the art.

Based on the foregoing, the claims are definite within the meaning of 35 U.S.C. §112, second paragraph. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claim 1 under 35 U.S.C. §102(b) over Anderson et al. (U.S. patent No. 5,476,966) is respectfully traversed.

Anderson et al. describe decreasing intracellular glutathione levels in cells and tissue in order to avoid detoxification of drugs through formation of glutathione S-conjugates. The reference states that increased glutathione levels seem to be a factor in tumor-cellular resistance to anti-cancer drugs (chemotherapeutic agents), which are detoxified by forming a conjugate with glutathione after being incorporated, and that, by administering certain compounds which inhibit glutathione synthesis, depletion of glutathione enhances the effect of cancer chemotherapy. Thus, Anderson et al. describe the content of glutathione in cancer cells but not in immune cells, and the reference only mentions the deprivation of chemotherapeutic agents by conjugation with glutathione. Anderson et al. do not disclose or suggest the effect of intracellular content of glutathione on immune responses. Needless to say, the reference does not suggest the useful method of preventing immunological diseases

due to reduction of cellular immunity by increasing IL-6 production and decreasing IL-12 and NO production in macrophages by administering to a patient a composition containing a substance which reduces the content of reductive glutathione in macrophages. Therefore, the reference does not describe the claimed invention. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the application is in condition for allowance. Early notice of such action is earnestly solicited.

Respectfully submitted,

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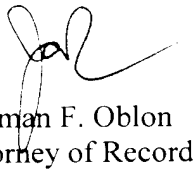

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IN THE CLAIMS

Please cancel Claims 3 and 11.

Please amend the claims as follows.

--1. (Twice Amended) A method of treating cachectic condition caused by cancers, diabetes, gastrointestinal inflammatory diseases, chronic rheumatoid arthritis, hepatitis, hepatic cirrhosis, hypersensitive interstitial pneumonia, pulmonary fibrosis or autoimmune inflammatory diseases, comprising administering to a patient in need thereof an effective amount of a composition comprising a substance, wherein said substance [which] (a) reduces the content of reductive glutathione in macrophages in said patient, [wherein said substance] (b) suppresses cellular immune responses in said patient, (c) increases IL-6 production by macrophages in said patient, and (d) decreases IL-12 and NO production by macrophages in said patient.

2. (Amended) The method of Claim 1, wherein the substance has an [a] intramolecular disulfide bond.

11. (Twice Amended) The method of [suppressing immune responses according to] Claim 1, wherein said substance [is a compound in which] is a conjugate of a cytotoxic DNA alkylating agent [is conjugated with] and glutathione, or one which shows cytotoxicity after being incorporated into macrophages as a precursor.--

Please add the following claims.

--20. (New)

21. (New)

22. (New)

23. (New)

24. (New)

25. (New)

26. (New)

27. (New)

28. (New)

29. (New)